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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/009,897	12/14/2001	Shingo Kato	Q 67685	4572

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EXAMINER	
GOLDBERG, JEANINE ANNE	
ART UNIT	**PAPER NUMBER**
1634	

DATE MAILED: 06/24/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/009,897	KATO ET AL.	
	Examiner	Art Unit	
	Jeanine A Goldberg	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *10 December 2003*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-18* is/are pending in the application.

4a) Of the above claim(s) *13,17 and 18* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-12 and 14-16* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☒ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. This action is in response to the papers filed December 10, 2003 Currently, claims 1-18 are pending. Claims 13, 17-18 have been withdrawn as drawn to non-elected subject matter.

Election/Restrictions

2. Restriction is required under 35 U.S.C. 121 and 372.

This application contains the following inventions or groups of inventions which are not so linked as to form a single general inventive concept under PCT Rule 13.1.

In accordance with 37 CFR 1.499, applicant is required, in reply to this action, to elect a single invention to which the claims must be restricted.

Group I, claim(s) 1-17, drawn to methods of determining HIV-1 subtypes by amplifying a portion of the env gene of HIV-1.

Group II, claim(s) 18, drawn to a kit comprising primer pairs.

3. The inventions listed as Groups I-II do not relate to a single general inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, they lack the same or corresponding special technical features for the following reasons.

According to PCT Rule 13.2, unity of invention exists only when there is a shared same or corresponding special technical feature is a contribution over the prior art. The inventions listed in Group I do not relate to a single general inventive concept because the lack of the same or corresponding special technical feature. The technical feature of Group I is "the env gene of HIV-1" which is shown by Korber et al (Human Retroviruses and AIDS 1992) to lack novelty or inventive step and does not make it a contribution over the prior art. Applicant is required to select a single combination of primers for examination. The combination may require a single pair or a combination comprising all possible pairs.

4. During a telephone conversation with Gordon Kit on May 30, 2003 a provisional election was made with traverse to prosecute the invention of Group I, primers of SEQ

ID NO: 20 and 28 directed to subtype B, claims 1-12, 14-16. Affirmation of this election must be made by applicant in replying to this Office action. Claims 13, 17-18 are withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being drawn to a non-elected invention.

5. Applicant is reminded that upon the cancellation of claims to a non-elected invention, the inventorship must be amended in compliance with 37 CFR 1.48(b) if one or more of the currently named inventors is no longer an inventor of at least one claim remaining in the application. Any amendment of inventorship must be accompanied by a request under 37 CFR 1.48(b) and by the fee required under 37 CFR 1.17(i).

Priority

6. This application claims priority to Japanese documents 11/167736 and 2000/23581. It is noted that no translation of these documents has been filed.

Should applicant desire to obtain the benefit of foreign priority under 35 U.S.C. 119(a)-(d) prior to declaration of an interference, a translation of the foreign application should be submitted under 37 CFR 1.55 in reply to this action.

Drawings

7. The drawings are objected to since they do not contain a sequence identifier following the primer sequences.

This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 CFR 1.821(a)(1) and (a)(2). However, this application fails to comply with the requirements of 37 CFR 1.821 through 1.825.

Claim Rejections - 35 USC § 112- Second Paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

8. Claims 7, 9 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

A) Claims 7 and 9 are indefinite over the recitation (primer 1), (nucleotide sequence 1), (primer 2) and (nucleotide sequence 2) because it is unclear how these parentheticals further limit the claim. It is unclear whether the parentheticals are merely directed to preferred embodiments or whether the claims require the recitation within the parentheticals.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

9. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

10. Claims 1-10, 12, 14-16 are rejected under 35 U.S.C. 103(a) as being unpatentable over Barbosa et al (Tranfus. Sci. Vol. 19, No. 1, pages 39-43, 1998) in view of Wang et al (US PgPub 2002/0106639, August 2002) and Korber Human Retroviruses and AIDS (1992 and 1997) and Hogan (US Pat. 5,595,874, Jan 1997).

Barbosa et al. (herein referred to as Barbosa) teaches a method of distinguishing between HIV-1 subtypes (A to I) using PCR and heteroduplex mobility. Barbosa teaches PCR amplification of HIV-1 env gene regions. Barbosa teaches that the method is able to distinguish between individual strains and may also provide

reliable information for phylogenetic analysis (page 40, col. 1). Barbosa teaches using the env gene comprising the C2 and C3 region. The PCR primers used are directed to various regions of the env gene. It is noted positions 7001-7020 are the same regions identified by Delwart et al. (Methods : A companion to Methods in Enzymology, Vol. 12, pages 348-354, 1997) using ED7 primer (page 350) which is SEQ ID NO: 20.

Barbosa does not specifically teach a method for determining HIV-1 subtypes which relies upon different pairs or primers for different HIV-1 subtypes.

However, Wang et al (US PgPub 2002/0106639, August 2002) teaches methods of detecting subtypes of PCV using a comparison alignment of PCV1 and PCVII. The multiplex PCR assay used for the detection of PCV identified and distinguished between the presence of the two isolates PCVI and PCVII. (see Figure 5 and 6)(para 30 and 31). A comparison between the viral genomes indicates that the genomes share approximately 76% identity (para 79). For the multiplex primers, two primers were designed to identify the PCV group-specific sequences and strain-specific sequences (para 168). Example 6 illustrates multiplex PCR in PCVII identification. Wang teaches that "in order to differentiate the two strains of porcine circoviruses, PCVI and PCVII, two sets of primers were designed based upon the comparative analysis of the viral DNA sequences" (para 194).

Further, both Korber 1992 and Korber 1997 teach HIV genomic sequences from various subtypes of the env gene. The 1992 alignment provides a "consensus" sequence for Subtype A, B, C, D, E, O. The 1997 alignment provides more information over the genomic sequence. Each of these sequences comprises SEQ ID NO: 20.

However, Hogan et al. (herein referred to as Hogan) teaches a method of preparing nucleic acids for assays which allow for distinguishing organisms. Hogan teaches that "we can confidently design probes based on a few rRNA sequences which differ between the target organism and its phylogenetically closest relatives" (col. 6, lines 35-45). Hogan teaches the use of specific primers col. 6-7, lines 50-67, lines 1-12, and furthermore provides specific guidance for the selection of primers,

> "Once the variable regions are identified, the sequences are aligned to reveal areas of maximum homology or 'match'. At this point, the sequences are examined to identify potential probe regions. Two important objectives in designing a probe are to maximize homology to the target sequence(s) (greater than 90% homology is recommended) and to minimize homology to non-target sequence(s) (less than 90% homology to non-targets is recommended). We have identified the following useful guidelines for designing probes with the desired characteristics.
> First, probes should be positioned so as to minimize the stability of the probe:nontarget nucleic acid hybrid. This may be accomplished by minimizing the length of perfect complementarity to non-target organisms, avoiding G and C rich regions of homology to non-target sequences, and by positioning the probe to span as many destabilizing mismatches as possible (for example, dG:rU base pairs are less destabilizing than some others). Second, the stability of the probe:target nucleic acid hybrid should be maximized. This may be accomplished by avoiding long A and T rich sequences, by terminating the hybrids with G:C base pairs and by designing the probe with an appropriate Tm. The beginning and end points of the probe should be chosen so that the length and %G and %C result in a Tm about 2-10°C higher than the temperature at which the final assay will be performed. The importance and effect of various assay conditions will be explained further herein. Third, regions of the rRNA which are known to form strong structures inhibitory to hybridization are less preferred. Finally, probes with extensive self complementarity should be avoided."

Therefore, it would have been prima facie obvious to one of ordinary skill at the time the invention was made to have modified the methods of Barbosa directed to distinguishing between HIV-1 subtypes with the method of Wang who uses multiplexing

with two sets of primers specific to particular subtypes to distinguish two viral genomic sequences. The art teaches the important to distinguish between HIV-1 subtypes A-I for reliable genetic screening as well as for phylogenetic analysis, see Barbosa. The ordinary artisan would have recognized the art demonstrated methods for distinguishing between subtypes and isolates. The art teaches multiplex methods for distinguishing between viral genome isolates which includes using primer pairs specific to the distinct isolates. The ordinary artisan would have been motivated to have used the multiplex method of Wang for the expected benefits of multiplex methods which include saving on reagents, utilizing less sample and efficiency. Since two primer pairs are combined into a single assay, the assay requires less reagents, utilizes less sample and requires less technician time for preparation. Thus, the ordinary artisan would have been motivated to have developed a multiplex PCR assay for distinguishing two or more viral genomic sequences from HIV-1 for example. The art provides alignment comparisons between HIV subtypes (see Korber). Thus, the ordinary artisan would have been motivated to have designed primers for the multiplex amplification "in order to differentiate" the strains, subtypes or isolates of HIV-1. Hogan provides specific teachings how to differentiate between regions of interest and non-interest. Designing probes and primers to know aligned regions for differentiation of subtypes was routine in the art at the time the invention was made. Hogan provides particular guidelines to selecting probes and primers which may be used to detect a particular target at the exclusion of all other targets. The ordinary artisan would have been motivated to have generated primer pairs for the multiplex method of Wang using the primer design guidelines of

Hogan. Barbosa teaches using the env gene comprising the C2 and C3 region. Therefore, the ordinary artisan would have been motivated to have targeted the known region for distinguishing subtypes of HIV-1. Furthermore, the ordinary artisan would have been motivated to have chosen a nucleic acid control which was present in all subtypes and universal to HIV-1 to ensure the positive control existed to ensure the effectiveness of the amplification. Hogan teaches determining primers to regions which are conserved among multiple subtypes and isolates. Therefore, designing a positive control to ensure the fidelity of the assay would have been obvious to the ordinary artisan at the time the invention was made.

Allowable Subject Matter

11. A search of the art fails to identify a sequence from subtype B which comprises both SEQ ID NO: 20 and 28 such that it would be obvious to use the primer pair of a nucleic acid consisting of SEQ ID NO: 20 and 28 to identify subtype B. While the art teaches HIV-1 sequences comprising SEQ ID NO: 28, the art does not teach these sequences are HIV-1 subtype B, therefore, there would be no motivation to use a primer consisting of SEQ ID NO: 28 in combination with a primer consisting of SEQ ID NO: 20.

Conclusion

12. No claims allowable.

13. The art made of record and not relied upon is considered pertinent to applicant's disclosure.

A) Delwart et al. (Methods : A companion to Methods in Enzymology, Vol. 12, pages 348-354, 1997) teaches amplifying HIV using ED7 primer (page 350) which is SEQ ID NO: 20.

B) Hahn (US Pat. 6,492,110, December 10, 2002) teaches an alignment of various HIV-1 subtypes and methods of distinguishing HIV-1 subtypes.

C) Gonzalez-Villasenor (Mol. And Cell. Probes, Vol. 14, pages 137-147, July 2000) teaches a solid phase plate assay for HIV-1 genotyping subtypes. It is noted that the availability of this paper is after the international filing date of June 16, 2000.

D) Klein (WO 00/44935, August 2000) teaches multiplex real-time PCR for amplifying multiple isolates in a single sample. It is noted that this art is not prior art.

14. Any inquiry concerning this communication or earlier communications from the examiner should be directed to examiner Jeanine Goldberg whose telephone number is (571) 272-0743. The examiner can normally be reached Monday-Friday from 8:00 a.m. to 4:00 p.m.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Jones, can be reached on (571) 272-0745.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

J. Goldberg

Jeanine Goldberg
Patent Examiner
June 22, 2004